



THE TRANSMITTER

November 2014

Article Review

Prepared by: Jessica Lehosit, DO, William Carne, PhD, & Abu A Qutubuddin, MD, M.B.B.S.

Randomized Withdrawal Study of Patients With Symptomatic Neurogenic Orthostatic Hypotension Responsive to Droxidopa.

The aim of this study was to evaluate whether droxidopa, a prodrug converted to norepinephrine, is beneficial in the treatment of symptomatic neurogenic orthostatic hypotension, which results from failure to generate an appropriate norepinephrine response to postural challenge. Patients with symptomatic neurogenic orthostatic hypotension and Parkinson disease, multiple system atrophy, pure autonomic failure, or non-diabetic autonomic neuropathy underwent open-label droxidopa titration (100-600 mg, 3× daily). Responders then received an additional 7-day open-label treatment at their individualized dose. Patients were subsequently randomized to continue with droxidopa or withdraw to placebo for 14 days. Patient-reported scores were assessed on the Orthostatic Hypotension Questionnaire and blood pressure measurements. Mean worsening of Orthostatic Hypotension Questionnaire dizziness/lightheadedness score from randomization to end of study (the primary outcome; N=101) was 1.9 ± 3.2 with placebo and 1.3 ± 2.8 units with droxidopa ($P=0.509$). Four of the other five Orthostatic Hypotension Questionnaire symptom scores and all 4 symptom-impact scores favored droxidopa, with statistical significance for the patient's self-reported ability to perform activities requiring standing a short time ($P=0.033$) and standing a long time ($P=0.028$). Furthermore, a post hoc analysis of a predefined composite score of all symptoms (Orthostatic Hypotension Questionnaire composite) demonstrated a significant benefit for droxidopa ($P=0.013$). There was no significant difference between groups for standing systolic blood pressure ($P=0.680$). Droxidopa was well tolerated. In summary, this randomized withdrawal droxidopa study failed to meet its primary efficacy end point. Additional clinical trials are needed to confirm that droxidopa is beneficial in symptomatic neurogenic orthostatic hypotension, as suggested by the positive secondary outcomes of this trial.

[Hypertension](#). 2014 Oct 27. pii: HYPERTENSIONAHA.114.04035. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/25350981>

Parkinson disease and smoking revisited: Ease of quitting is an early sign of the disease

The authors explore the counter-intuitive findings that tobacco use appears to be neuroprotective against PD. They note that selection bias, confounding, and/or measurement error cannot be used to explain this phenomenon. They hypothesized that mechanisms responsible for PD may also play a role in smoking avoidance or unproblematic cessation of early tobacco use and lead these individuals to tobacco-free lifestyles. Using a case-control design they matched 1808 patients from Danish registries with PD (diagnosed between 1996-2009; diagnosis confirmed by a movement disorder specialist) with 1876 population controls on sex and year of birth and collected lifestyle information including lifelong smoking history and nicotine replacement, in a structured telephone interview. They estimated odds ratios and 95% confidence intervals with logistic regression adjusting for matching factors and confounders.

Results suggested that fewer patients with PD than controls ever established a smoking habit. Among former smokers, those with greater difficulty quitting or using nicotine substitutes were less likely to develop PD, with the risk being lowest among those reporting “extremely difficult to quit” compared with “easy to quit.” Nicotine substitute usage was strongly associated with quitting difficulty and duration of smoking, i.e., most strongly among current smokers, followed by former smokers who had used nicotine substitutes, and less strongly among former smokers who never used substitutes.

The authors conclude that patients with PD are able to quit smoking more easily than controls, and propose that ease of smoking cessation is an aspect of on-coming PD similar to olfactory dysfunction, REM sleep disorders, or constipation and suggests that the apparent “neuroprotective” effect of smoking observed in epidemiologic studies is due to reverse causation..

[Neurology](http://www.ncbi.nlm.nih.gov/pubmed/25217056). 2014 Oct 14;83(16):1396-402. doi: 10.1212/WNL.0000000000000879. Epub 2014 Sep 12
<http://www.ncbi.nlm.nih.gov/pubmed/25217056>

High-Frequency Oscillations in Parkinson’s Disease: Spatial Distribution and Clinical Relevance

Abnormal oscillatory activities of the basal ganglia plays an important role in Parkinson’s disease (PD). Pathophysiology of PD has been related to excessive beta band oscillations mostly in basal ganglia. Beta frequency band 13-35 Hz considered a biomarker of akinesia. Research has recently focused on high-frequency oscillations >200 Hz observed in subthalamic nucleus (STN) and globus pallidus internus(Gpi). Both of these structures are effective deep brain stimulator (DBS) targets for the treatment of PD. High frequency oscillation (HFO) has also shown to increase with movement initiation and decreases with movement cessation. HFOs were suggested to reflect the motor state. Little is known about the characteristics and functional properties of these oscillations. This research paper showed that the team studied 10 PD patients in medication off state who underwent DBS surgery. Intraoperatively 5 channel microelectrode recordings were performed at 9-10 recording sites within STN and its immediate vicinity. They found a focal spatial distribution of HFO with highest power 2mm below the dorsolateral border of the STN. The results of these scientists demonstrated a focal origin of high-frequency oscillations within the STN and provide further evidence for their functional association with motor state.

[Mov Disord](http://www.ncbi.nlm.nih.gov/pubmed/25041924). 2014 Sep;29(10):1265-72. doi: 10.1002/mds.25962. Epub 2014 Jul 10
<http://www.ncbi.nlm.nih.gov/pubmed/25041924>

Committee Activities

Clinical Care Committee

- **Rotation of Committee Chair:** Leadership for the clinical care committee rotates amongst the PADRECCs. The Northwest PADRECC leads the committee for November/December. Committee meets via conference call the first Tuesday of the month at 12pm (EST)
- **Standardize and Optimize Clinical Care:** Continues to discuss a variety of clinical issues to learn from each other’s experience, establish usage patterns of existing and emerging therapies, and discuss ways to enhance overall patient care. The committee continues to provide clinical support to the Consortium network, and work on measures to standardize clinical care across the PADRECC network. Recent agenda items have included ongoing discussion on:
 - Use of Clinical Video Telehealth for movement disorders and home monitoring devices: Review of applications in clinical arena for subset of patients, and ways to expand access to CBOCs and remote areas where subspecialty expertise is not available. Research ideas pertaining to the use of home monitoring devices in movement disorders patients.
 - Palliative Care: Review of palliative care resources in the PADRECCs and potentially working together to provide resources to guide a fellow interested in the area of palliative care issues in the movement disorder patient

- Therapy Topics: DBS target selection, Experience with various Neurotoxins, Use of newer anti-PD formulations (e.g. Neupro Patch) across the PADRECC's etc.
- Quality improvement/assurance project looking at hospitalized PADRECC patients and use of dopamine-blocking medications
- The use of DAT scans in clinical practice: Applications and pitfalls of use. Standardization of reads
- The incorporation of yoga and other exercise modalities along with meditation and breathing in the care of the PD patient and how to enhance access of these modalities to our patients
- **PADRECC Transmitter:** PADRECC clinicians provide reviews of recent movement disorder publications that are included in the PADRECC Transmitter

Education Committee

- **PADRECC/EES Movement Disorder Series:** The 1st audio conference for FY 15 was held on **November 13, 2104** "Rehabilitation Tools & Practices for Common Movement Disorder Diseases." The audio conferences are archived on the National website www.parkinsons.va.gov under the Movement Disorder Series tab. All evaluations for CMEs are being done electronically via TMS and preregistration is required. Please see the **Dates to Remember** section below for listing of upcoming audio conferences.
- **Patient Education Video Project:** The My Parkinson's Story video series from FY 11 & 12 are now available for viewing on the National PADRECC & VA Consortium Website: <http://www.parkinsons.va.gov/patients.asp> and on You Tube.
- **Enduring Materials Project:** In collaboration with EES, the committee developed an on-line TMS self-study program that offers CME credit for a 3 year period. The purpose of this program is to provide VHA healthcare professionals with a broadened medical awareness of **Mood Disorders in PD**. The program is **NOW** available on TMS:

https://www.tms.va.gov/learning/user/deeplink_redirect.jsp?linkId=ITEM_DETAILS&componentID=14771&componentTypeID=VA&revisionDate=1343926380000
- **National Newsletter:** The National Newsletter is complete and available for viewing on the National PADRECC & VA Consortium Website:
- **PADRECC Transmitter:** The committee continues to assemble and distribute this e-newsletter every other month.

Southeast PADRECC Service Area Updates

North Florida/South Georgia VAMC, Gainesville, FL

Director: Christopher Hess, MD

Phone: 352-374-6058

The North Florida/South Georgia (NF/SG) Consortium Center provides care to veterans with Parkinson's disease as well as a variety of other movement disorders, including atypical parkinsonism, tremor disorders, myoclonus, chorea, dystonia, ataxia, and functional movement disorders. They provide EMG-guided botulinum toxin injections for movement disorders, as well as patient selection, programming, and follow-up care for patients requiring deep brain stimulation. A movements disorders physiology laboratory is being established to aid in patient diagnosis, capable of physiologic studies such as tremor analysis, EMG-EEG back-averaging, blink-reflex recovery analysis, and transcranial magnetic stimulation (TMS) measurement of central motor conduction times. Dr. Hess recently spoke at the Association of VA Speech-Language Pathologists (AVASLP) National Meeting and gave a nationally broadcast webinar for the National Parkinson Foundation (NPF) on pain and fatigue in Parkinson's disease.

Atlanta VAMC, Decatur, GA

Director: Marian L. Evatt, MD MS

Phone: 404-235-3077

The Movement Disorders Clinic was established in 2005 and is staffed by Neurologist, Dr. Marian Evatt, Neurology Nurse Coordinator J.Renee Livsey, and Nurse Practitioner Pamela Brown. It provides subspecialty consultations for movement disorders, patient selection and management services for DBS surgery, and botulinum toxin injections. Dr. Evatt is affiliated with the Emory University and the Emory Parkinson's Disease Research Center and serves as the PI clinical/translational studies that recruit subjects through the Atlanta VAMC Movement Disorders Clinic. The Atlanta Consortium Center also works with American Parkinson's Disease Association (APDA) Information and Referral Center at Emory and the National Parkinson's Foundation (NPF) Center of Excellence at Emory to provide patient education and support activities. Dr. Evatt was an invited speaker at two educational sessions recently: September 27 in Atlanta on essential tremor for patients and caregivers, and October 11 in Richmond, VA on nutritional issues at the annual Parkinson's disease community education day.

Movement Disorders Clinic Referrals: Due to high demand, the Atlanta VA Neurology Clinic is currently advising providers to refer patients from VA Centers other than the Atlanta VAMC to local non-VA fee basis providers. However, providers may contact Dr. Evatt for general advice on management of movement disorders. Dr. Evatt is currently working to establish video tele-health clinic follow up visits for patients with movement disorders.

Lexington VAMC, Lexington, KY

Director: John T. Slevin, MD

Phone: 859-281-4920

Established in 2000, the Movement Disorders Clinic is staffed by Dr. Slevin, a nurse practitioner, a movement disorders fellow and Pharm. D. It provides subspecialty consultations, patient selection and management services for DBS surgery, and botulinum toxin injections. Dr. Slevin is affiliated with the University of Kentucky Medical Center and Director of Clinical Research for the UKMC Parkinson's Disease Research Center of Excellence. He is the PI or Co-PI on 3 industry, 1 investigator initiated and 1 NIH-sponsored clinical/translational studies, two of which are currently recruiting subjects.

Recent Publications from this Consortium Site:

- Moonen, A.J. et al. *Severity of depression and anxiety are predictors of response to antidepressant treatment in Parkinson's disease*. Parkinsonism & Related Disorders 20:644-46, 2014. doi:S1353-8020(14)00078-9[pil]10.1016/j.parkreldis.2014.02.025. Epub 2014 Apr 01.
- Stephens, M., Bensalem Owen, M.K., SLEVIN, J.T., Pomerleau, F., Heuttl, P., Gerhardt, G.A. *Tonic glutamate in CA1 of aging rats correlates with phasic glutamate dysregulation during seizure*. Epilepsia, in press.

- Andersen, A.H., Smith, C.D., SLEVIN, J.T., Kryscio, R.J., Martin, C.A., Schmitt, F.A. and Blonder, L.X. *Dopaminergic modulation of medial prefrontal cortex deactivation in Parkinson depression*. PLoS One, submitted.
- SLEVIN, J.T., Fernandez, H.H., Zadikoff, C., Hall, C., Eaton, S., Dubow, J., Chatamra, K. and Benesh, J. *Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: An open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients*. Parkinsonism & Related Disorders, submitted.
- Bailey J, Ryan M, Steinke D, SLEVIN JT, Kasarskis EJ. *Valproic acid and parkinsonian symptoms in a Veterans Affairs population*. Pharmacoevidence and Drug Safety. submitted.
- Xu, G. *et al.* and the Gene-PD Study Group. *R.H. Type-1 Protein Phosphatase Inhibitor 4 (I-4) on Xp11.4-11.3 is Associated with Familial and Idiopathic Parkinson's disease: The GenePD Study*. American Journal of Human Genetics, submitted.
- Nagle, M.W. *et al.* and the Gene-PD Study Group. *Polymorphisms and Expression in SIRT3 are associated with Parkinson disease: the GenePD Study*. Neurology, submitted.

Dates to Remember

January 8, 2015

EES/PADRECC Movement Disorder Series

Topic: A Systematic Approach to the Patient with Chorea

<http://www.parkinsons.va.gov/>

March 12, 2015

EES/PADRECC Movement Disorder Series

Topic: TBA

<http://www.parkinsons.va.gov/>

March 23-25, 2015

2015 PAN Forum

Washington, DC

<http://www.parkinsonsaction.org/your-voice/pan-conference>

April 18-25, 2015

American Academy of Neurology Annual Meeting

Washington, DC

<https://www.aan.com/conferences/2015-annual-meeting/submit-your-abstract/>

May 14, 2015

EES/PADRECC Movement Disorder Series

Topic: Tardive Dyskinesia

<http://www.parkinsons.va.gov/>

June 14-18, 2015

25th Annual Movement Disorder Society International Congress

San Diego, CA

<http://www.movementdisorders.org/MDS.htm>

September 10, 2015

EES/PADRECC Movement Disorder Series

Topic: TBA

<http://www.parkinsons.va.gov/>